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Timing of lowest and highest peak expiratory flow in patients with asthma: influence of anti-inflammatory treatment

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We sought to determine the optimal time for measuring peak expiratory flow rate (PEF) in patients with mild to moderate asthma, before and after treatment with inhaled beclomethasone dipropionate (BDP). After 2 weeks of observation, BDP (400 μg/d) was given to 22 patients with mild to moderate asthma. The dose of BDP (800–1200 μg/d) was increased every 2 weeks until PEF varied by no more than 20% each day. PEF was measured four times daily: on awakening, around noon, in the evening and at bedtime. Significant ($P<0{\cdot}05$) rhythms were detected by single cosinor analysis in all patients, both during observation and during treatment. Analysis by the population mean–cosinor method showed that the mean mesor was $378{\cdot}8\pm59{\cdot}1$ l min^{-1}, the mean amplitude was $53{\cdot}9\pm13{\cdot}4$ l min^{-1}, and the mean acrophase was at $16{:}26\pm0{:}32$ before treatment. After treatment, the mean mesor was $528{\cdot}0\pm61{\cdot}9$ l min^{-1}, the mean amplitude was $37{\cdot}6\pm12{\cdot}2$ l min^{-1}, and the mean acrophase was at $16{:}35\pm0{:}32$. The mesor increased significantly ($P<0{\cdot}05$), and the amplitude decreased significantly ($P<0{\cdot}05$) after treatment. The acrophase did not change. These data indicate that PEF is lowest at 04:30 and highest at 16:30 in patients with mild to moderate asthma, both during observation and during treatment. We conclude that if one needs to assess PEF twice a day, this should ideally be done at 04:30 and 16:30, not only before but also after treatment with BDP.

Key words: asthma; peak expiratory flow rate; beclomethsone dipropionate.

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Introduction

Increasing morbidity and mortality from asthma (1) have prompted the development of various means for monitoring the severity of this disease. Home peak expiratory flow (PEF) monitoring is a widely recommended technique helpful in the diagnosis and management of asthma that can provide information about day-to-day airway lability. PEF measurements are simple, quantitative and reproducible, and correlate well with FEV_1 as measured by spirometry (2,3). In the individual asthmatic patient, home PEF monitoring helps to assess the degree of airflow obstruction and overall severity of disease. Many PEF indices have been proposed and tested, and daily PEF variability is most commonly used for the management of asthma. PEF is as satisfactory as FEV_1 for describing circadian variation among normal subjects and stable patients with asthma (4). In most studies, patients inhaled β-agonists two to four times daily (5), but regular use of inhaled β-agonists does not comply with current therapeutic guidelines, which recommend that β-agonists should be inhaled as needed to relieve asthma symptoms. Accurate evaluation of daily PEF variability requires that PEF is measured twice daily, at the times of the lowest and highest values. To our knowledge, however, no study has determined whether or not the timing of the lowest and highest daily PEF values is altered by inhaled steroids in asthmatic patients.

Cosinor analysis has been used to evaluate circadian rhythms of pulmonary function in normal and asthmatic subjects. Circadian rhythms have previously been detected, not only in normal subjects but also in patients with asthma. Asthma may be associated with an exaggerated normal circadian rhythm (6). We investigated the optimal time for measuring PEF in patients with mild to moderate asthma who received inhaled β-agonists as needed, both before and after treatment with inhaled beclomethasone dipropionate (BDP).

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Materials and methods

SUBJECTS

Patients with mild to moderate asthma ($FEV_1 > 60\%$ predicted) who had received no previous treatment were entered into this study. Smokers and patients with severe asthma ($FEV_1 \leq 60\%$ predicted) were excluded. All enrolled patients met the American Thoracic Society diagnostic criteria for asthma (7). PEF was measured throughout the study.

PEF MEASUREMENT

Patients were instructed in the use of a peak flow meter (Assess, Healthscan Products Inc., Cedar Grove, New Jersey, U.S.A.), and were requested to record their PEF values and the time of measurement throughout the study. We carefully instructed patients on how to use a peak flow meter as follows: 'Do the following five steps with your peak flow meter: (i) move the indicator to the bottom of the numbered scale; (ii) stand up; (iii) take a deep breath, filling your lungs completely; (iv) place the mouthpiece in your mouth and close your lips around it: do not put your tongue inside the hole; (v) blow out as hard and fast as you can in a single blow; write down the number you get, but if you cough or make a mistake, don't write down the number, do it over again.' The patients recorded the value and time of the best of three expirations four times daily, on awakening, around noon, in the evening and at bedtime, before inhaling a β-agonist as needed for symptoms. If the patient inhaled a β-agonist on demand, PEF was measured 4 h or more after administration. Daily PEF variability was calculated according to the following formula: [(highest PEF − lowest PEF)/mean PEF] (%).

STUDY DESIGN

After 2 weeks of observation, BDP 400 μg/d was given to the patients for 14 days. The effect of BDP 400 μg/d was evaluated on the basis of daily PEF variability and symptoms on the 12th, 13th and 14th days of treatment. If daily PEF variability was no more than 20% or symptoms disappeared, BDP 400 μg day^{-1} was continued; if daily PEF variability was more than 20% or symptoms persisted, the dose of BDP was increased to 800 μg day^{-1}. The effect of BDP 800 μg day^{-1} was evaluated on the basis of daily PEF variability and symptoms on the 12th, 13th and 14th days of treatment. If daily PEF variability was no more than 20% or symptoms disappeared, BDP 800 μg day^{-1} was continued; if daily PEF variability was more than 20% or symptoms persisted, the dose of BDP was increased to 1200 μg day^{-1} (Fig. 1). BDP was inhaled by means of a spacer device (Inspir Ease, Schering-Plough K.K., Osaka, Japan) four times daily after measuring PEF. A β-agonist (procaterol) was taken as needed for symptoms, not regularly, during the study.

STATISTICAL ANALYSIS

Results are expressed as means ± SE. Values of $P \leq 0{\cdot}05$ were considered to indicate statistical significance. We used cosinor analysis to assess the circadian rhythm of PEF. Cosinor analysis uses a least-squares method to test the goodness of fit of the raw data to a sinusoidal waveform to evaluate the characteristics of rhythms. Cosinor analysis involves three variables, mesor (value about which oscillation occurs), amplitude (half the difference between the highest and lowest values) and acrophase (timing of high point, in degrees) (Fig. 2). This method permits a quantitative definition of rhythms in individuals, specific groups, or populations. Single cosinor analysis finds its most obvious application in analysing a single series of values from an individual. A comparison of individual rhythms can be made on the basis of such analyses. Group mean–cosinor analysis is used for comparison of rhythms between specific groups, and population mean–cosinor analysis for comparison between populations, based on data obtained by cosinor analyses (6,8,9). The hypothesis that the amplitude is zero can be reflected with $P \leq 0{\cdot}05$, implying a statistically significant rhythm. We used single cosinor analysis to investigate the circadian rhythm of PEF, calculated on the basis of PEF and the times of measurement in each patient, both for the last 3 days of the 2 weeks observation period and for the last 3 days of the treatment period, i. e. after having achieved good control for at least 2

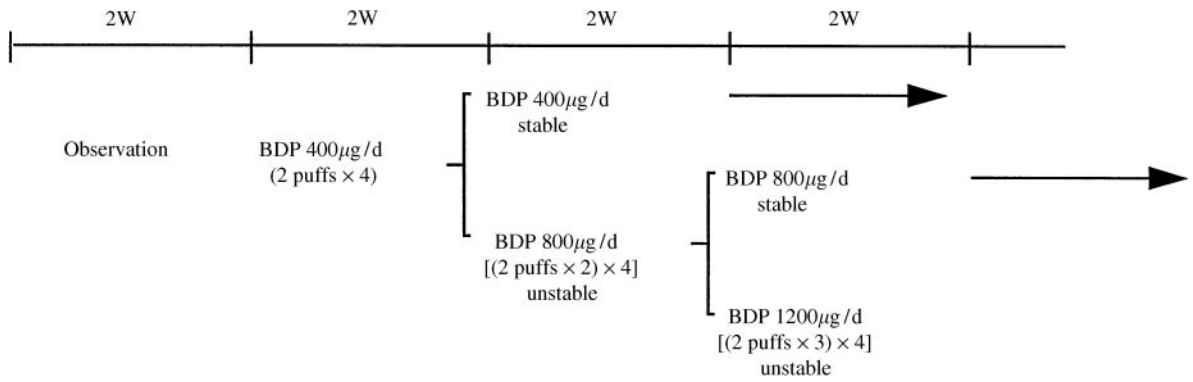

FIG. 1. Protocol. Stable: no symptoms or variability ≤20% on the 12th, 13th and 14th days of the BDP 400 or 800 μg day^{-1} treatment; unstable: symptoms or variability ≥20% on the 12th, 13th and 14th days of the BDP 400 or 800 μg day^{-1} treatment.

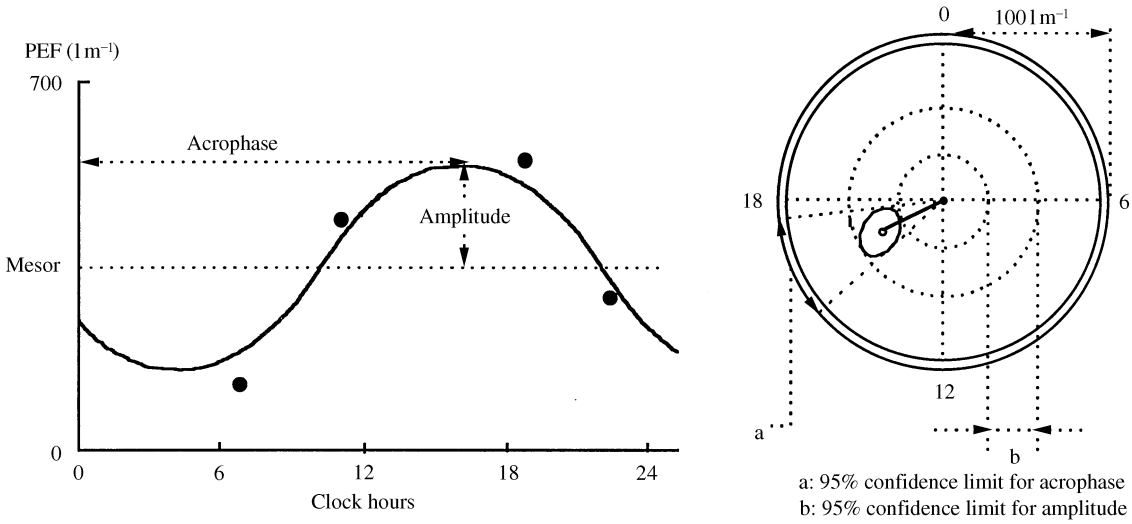

FIG. 2. Cosinor analysis. Rhythms are shown as vectors with length proportional to amplitude and angle indicating phase. Error ellipses enclose the 95% confidence limits for amplitude and phase. Scale: 100 l min^{-1}.

weeks. Good control was defined by the same criteria as those indicating continuation of the same dose of BDP. The circadian rhythm of PEF was investigated before and after treatment with BDP by group mean–cosinor analysis. In addition, we assessed the circadian rhythm of PEF before and after treatment with BDP by population mean–cosinor analysis, and we determined the most appropriate times to measure PEF twice daily.

Results

Table 1 lists the clinical characteristics of the patients (n=22) and the dose of BDP required for good control in the present study. Good control was obtained in all patients. FEV_1 obtained during good control was within the normal range in all patients. The mean dose of BDP required for good control was $1000 \pm 60{\cdot}3$ μg day^{-1} (range, 400–1200 μg day^{-1}). All patients had significant circadian rhythms detectable by single cosinor analysis, both during the observation and treatment periods. The mesor increased significantly in all except one patient, and the amplitude-acrophase changed significantly in seven patients (Table 2). Analysis by the group mean–cosinor method showed that the 95% confidence limit of the mean mesor was $378{\cdot}8 \pm 5{\cdot}8$ l min^{-1}, that of the mean amplitude was $53{\cdot}9 \pm 6{\cdot}2$ l min^{-1}, and that of the mean acrophase was at 16:26 $\pm$ 0:23 before treatment. After treatment, the 95% confidence limit of the mean mesor was $528{\cdot}0 \pm 3{\cdot}8$ l min^{-1}, that of the mean amplitude was $37{\cdot}6 \pm 4{\cdot}2$ l min^{-1}, and that of the mean acrophase was at 16:35 $\pm$ 0:22. The mesor test and the amplitude-acrophase test revealed significant differences between before and after treatment (Fig. 3). Population mean–cosinor analysis showed that the 95% confidence limit of the mean mesor was $378{\cdot}8 \pm 59{\cdot}1$ l min^{-1}, that of the mean amplitude was $53{\cdot}9 \pm 13{\cdot}4$ l min^{-1}, and that of the mean acrophase was at 16:26 $\pm$ 0:32. After treatment, the 95% confidence limit of the mean mesor was $528{\cdot}0 \pm 61{\cdot}9$ l min^{-1}, that of the mean amplitude was $37{\cdot}6 \pm 12{\cdot}2$ l min^{-1}, and that of the mean acrophase was at 16:35 $\pm$ 0:32 (Fig. 4). PEF was lowest at 04:30 h and highest at 16:30 h in patients with mild to moderate asthma, both before and after treatment with BDP. Patients with mild to moderate asthma had a circadian rhythm, both during the observation and treatment periods. The results of the mesor and the amplitude-acrophase tests were significant. The mean mesor increased significantly, and the mean amplitude decreased significantly after treatment. The mean acrophase did not change.

TABLE 1. Patient characteristics (n=22)

		n
Age (year)	$32{\cdot}0 \pm 3{\cdot}6$	
Range	16–69	
Sex		
Male: Female	18:4	
Smoking history		
Never smoker		21
Ex-smoker		1
Current smoker		0
Spirometry		
VC(l)	$3{\cdot}72 \pm 0{\cdot}42$	
%VC	$101{\cdot}3 \pm 9{\cdot}2$	
FEV_1(l)	$2{\cdot}58 \pm 0{\cdot}34$	
%FEV_1(l)	$67{\cdot}1 \pm 5{\cdot}2$	
Skin prick testing		
Atopic		11
Non-atopic		11
BDP dose (μg day^{-1})	$1000 \pm 60{\cdot}3$	
Range	400–1200	

TABLE 2. Single Cosinor Analysis of data collected during observation and during treatment with BDP (the mesor increased significantly in all except for one patient and the amplitude-acrophase changed significantly in seven patients)

Case	Observation			Treatment			Mesor test	Amplitude-acrophase test
	Mesor ($l\,m^{-1}$)	Amplitude ($l\,m^{-1}$)	Acrophase (h:m)	Mesor ($l\,m^{-1}$)	Amplitude ($l\,m^{-1}$)	Acrophase (h:m)		
1	171±12	29±12	16:48±1:28	629±17	35±17	16:13±1:40	s	n.s.
2	239±12	41±13	14:36±1:00	336±6	22±7	16:03±1:00	s	s
3	573±24	51±31	18:04±2:03	692±27	42±33	15:40±3:24	s	n.s.
4	689±17	60±18	14:52±1:01	797±5	9±5	15:39±2:10	s	s
5	224±12	47±12	16:30±0:58	260±10	13±11	14:56±2:54	s	s
6	201±20	50±22	16:49±1:32	349±14	33±15	16:27±1:32	s	n.s.
7	493±26	73±27	16:22±1:16	600±13	17±14	15:07±3:03	s	s
8	579±37	85±37	17:12±1:28	654±22	63±26	17:06±1:22	s	n.s.
9	407±29	69±28	16:50±1:25	578±15	46±18	17:30±1:13	s	n.s.
10	316±59	75±63	16:12±3:01	566±35	72±38	16:51±1:44	s	s
11	538±24	70±26	14:24±1:13	544±17	34±19	14:58±1:52	n.s.	n.s.
12	373±35	90±44	16:51±1:25	501±18	63±23	16:35±1:08	s	n.s.
13	398±30	41±34	17:15±3:00	556±16	36±18	17:38±1:38	s	n.s.
14	327±43	59±49	15:53±3:56	690±29	47±33	17:11±2:41	s	n.s.
15	435±67	87±80	17:00±4:24	730±17	67±20	17:46±0:54	s	n.s.
16	285±14	27±16	17:03±1:52	387±10	28±12	15:58±1:21	s	n.s.
17	350±9	30±10	16:38±1:05	417±5	10±6	15:17±2:09	s	s
18	275±15	61±16	16:51±0:54	414±10	26±11	16:47±1:25	s	s
19	309±21	49±22	16:03±1:30	466±11	56±13	16:11±0:44	s	n.s.
20	411±28	53±29	15:35±1:46	535±22	59±23	15:59±1:18	s	n.s.
21	422±13	35±13	17:07±1:21	510±10	34±10	17·08±1:06	s	n.s.
22	321±23	37±24	17:11±1:58	413±11	27±14	15:54±1:42	s	n.s.

Values are ±95% confidence limit.
s: significant ($P<0{\cdot}05$); n.s.: non-significant ($P>0{\cdot}05$)

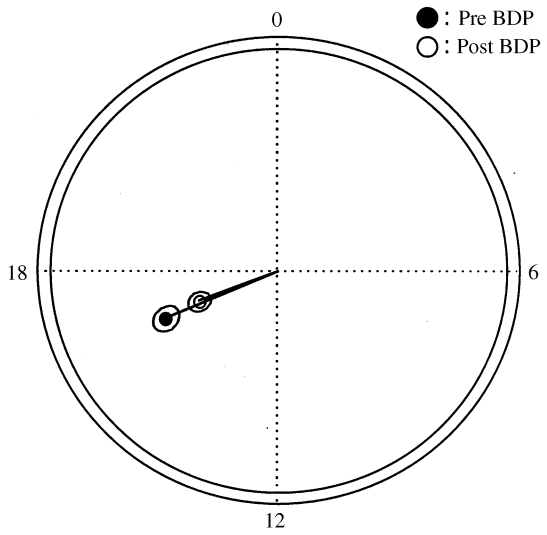

FIG. 3. Group mean–cosinor analysis. The mean acrophases are not significantly different between before and after treatmentwith BDP. N=26, Scale: 100 l min^{-1}.

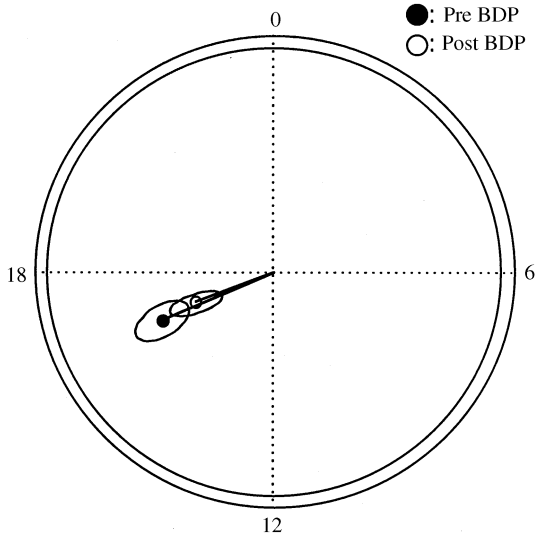

FIG. 4. Population mean–cosinor analysis. The mean acrophases are not significantly different between before and after treatment with BDP. N=26, Scale: 100 l min^{-1}.

Discussion

PEF measurement has been advocated for the objective assessment of asthma since the 1970s, when inexpensive and reliable portable devices became available (10), and is now widely used in the management of asthma (11–13). Because the measurement of PEF depends on effort and technique, patients require instruction, demonstration and frequent review of technique. We carefully showed patients how to use a peak flow meter. If one can use the device, quantification of PEF measurement is valuable in assessing the degree of airflow obstruction (14), disease severity (15) and daily variability in lung function. PEF can also be used to monitor the response to therapy (16), investigate specific allergens (17) and detect asymptomatic deterioration, which occurs in patients with severe asthma (18,19). PEF at a single point in time reflects airway obstruction in patients with asthma, but daily PEF variability is a marker of airway lability rather than of airway obstruction (20). Daily PEF variability is a useful index because the level of airway hyper-responsiveness usually correlates with the clinical severity of asthma as well as with medication requirements (21); moreover, fluctuations in morning and evening PEF correlate well with histamine-induced airway hyper-responsiveness (4,22). Recently, some reviews recommend that β-agonists should be inhaled as needed for symptoms, rather than regularly (11–13). To assess daily PEF variability in patients receiving inhaled β-agonists on an as-needed basis, we have to measure PEF twice daily, when PEF is lowest and highest.

Corticosteroids are currently the most effective anti-inflammatory drugs, and inhaled corticosteroids are widely used for the treatment of persistent asthma. Inhaled corticosteroids improve lung function (23–26), decrease airway hyper-responsiveness (23,24,26) and reduce symptoms (23,24,26) in patients with asthma. We used cosinor analysis to assess the circadian rhythms of PEF and to determine the optimal time for measuring PEF in patients with mild to moderate asthma, not only before but also after treatment with inhaled BDP. Cosinor analysis is commonly used to detect circadian rhythms. It may be inappropriate for the investigation of low amplitude circadian rhythm (27), but has the advantage of requiring only a small number of data for each rhythm cycle, provided the data are well distributed. The exact time of readings is also taken into account, so that any readings taken later than intended can still be used without impairing the accuracy of rhythm detection (6,8,9). Circadian rhythms have been demonstrated by cosinor analysis, both in normal subjects and in asthmatic patients (6,9). Hetzel and Clark reported that the mean acrophase was at 15:57 in asthmatic patients, but in their study patients were treated with corticosteroids or bronchodilators. Although circadian rhythms are predicted to be affected by bronchodilators, their results were close to our results in acrophase. In our study, each patient received only BDP at the minimal required for good control. All patients had circadian rhythms in PEF on single cosinor analysis, not only before but also after treatment with BDP. The circadian rhythms of PEF are predicted to be influenced by sleep patterns. However, in our study all patients worked during the daytime and there were no big differences in acrophases among patients on single cosinor analysis. Group mean–cosinor analysis and population mean–cosinor analysis detected circadian rhythms, both before and after treatment. These results imply that the group and the population with mild to moderate asthma had circadian rhythms before and after treatment with BDP. The mean-mesor increased significantly and the mean-amplitude decreased significantly after treatment, but the mean-acrophase did not change. The mean-acrophase was at $16{:}26 \pm 0{:}32$ before treatment and at $16{:}35 \pm 0{:}22$ after treatment. These results suggest that patients with mild to moderate asthma have circadian rhythms in PEF both before and after treatment with only BDP. It is very interesting that the acrophase does not change during treatment with BDP alone. In addition, in general, PEF is lowest at 04:30 h and highest at 16:30 h in patients with mild to moderate asthma. We conclude that if one needs to assess PEF twice a day, this should ideally be done at 04:30 h and 16:30 h, not only before but also after treatment with BDP. Practically speaking, it is recommended to measure PEF at a time close to 04:30 h, either on awakening or at bedtime, and at 16:30 h.

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